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(54) Title: A METHOD OF PREVENTING GASTROINTESTINAL SIDE-EFFECTS OF A DRUG OR FOOD PRODUCT

(57) Abstract: Methods of alleviating, reducing and/or preventing gastrointestinal (GI) side effects induced by a therapeutically and/or prophylactically active pharmaceutical substance or a food product in an animal including a mammal, the method comprising administration of one or more strontium containing compounds. Methods wherein the therapeutically and/or prophylactically active substance or food product responsible for/associated with the GI side effects is administered together with the one or more strontium containing compounds.

A Method of Preventing Gastrointestinal Side-Effects of a Drug or Food Product

Field of the Invention

The present invention relates to methods of alleviating or preventing potential GI side effects of a pharmaceutical product intended for oral administration or a food product by the administration of a strontium salt.

Background of the Invention

One major concern in the development of orally administered therapeutic products is the concern for gastrointestinal (GI) side effects mediated by the drug product. Such gastrointestinal side effects may include epigastric/abdominal pain, nausea, vomiting, diarrhea, dyspepsia, bloating, flatulence, anorexia, mucosal erosions and/or inflammation (esophagitis, gastritis, duodenitis, enteritis), gastrointestinal hemorrhage including hematemesis, melena and hematochezia, (peptic) ulcerations and GI strictures. Such GI side effects have been demonstrated for numerous drug classes such as non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, disease modifying anti-rheumatic drugs (DMARDs), glucocorticoids, cytostatic agents and others, that are used in used in treatment/prevention of malignant disease and others. The mechanisms by which these substances exert their GI toxicity range from a propensity to lower the pH of the stomach and intestinal lumen to potentials for inhibiting the physiological protective mechanisms of the epithelial cells of the stomach, as well as other mechanisms. In addition to a direct irritant effect on the mucosa, the common mechanism of many NSAIDs to inhibit the enzyme cyclo-oxygenase 1 (COX-1) is thought to be principally responsible for the gastrointestinal adverse effects of most NSAIDs, for which reason parenterally as well as enterally administered NSAIDs could exhibit said adverse GI effects. COX-1 is constitutively expressed as a 'housekeeping' enzyme in nearly all cells and tissues, and mediates physiological responses such as cytoprotection of the stomach.

NSAIDs, such as mixed COX1/COX2 inhibitors or more specific inhibitors of COX2 are used extensively for the management of acute and chronic pain, which is encountered in a wade range of diseases and conditions. In fact, the most common symptom associated with both chronic and acute diseases, disorders, trauma and medical conditions, is the presence of pain. Pain may be the symptom responsible for most physician visits, and pain is fundamental to medicine and in defining the well-being of individuals. Although all human beings will experience pain at some level in many

different situations, pain remains extremely difficult to define and quantify and the etiology of pain remains elusive. Aside from the physiological processes of pain induction, many psychological and psychosocial factors are related to adjustment to persistent pain. In the clinical management of pain, medications able to combat physiological processes involved in pain sensation either at peripheral sites or in the central nervous system (CNS) plays a central role, and analgesic /palliative medications remains some of the most prescribed drugs in use today. However, even with recent advances in the development of new palliative and analgesic agents, the medical interventions available today for the treatment of pain remains associated with substantial side effects, of which the propensity to induce GI related side-effects remains one of the most serious clinical problems.

Non-steroidal anti-inflammatory drugs (NSAID) comprise a heterogeneous group of compounds with an ability to reduce inflammatory signaling molecules such as prostaglandin synthesis and cyclo-oxygenase enzymes. NSAIDs are associated with significant side effects such as a gastrointestinal and cardiovascular complications. Conventional NSAIDs e.g. ibuprofen or naproxen, inhibit both isoforms of the cyclo-oxygenase enzyme i.e. COX-1 and COX-2 with almost equal potency. Inhibition of COX-1 is thought to be principally responsible for the gastrointestinal adverse effects of NSAIDs. As a result COX-2 specific inhibitors e.g. rofecoxib, celecoxib and valdecoxib were developed with aim of reducing GI related effects of the drug and block predominantly the COX-2 isoform, whilst the COX-1 isoform is largely spared. However, there is some uncertainty regarding the cardiovascular and renal effects of the COX-2 selective inhibitors, and these drugs are still associated with a significantly increased risk of GI side effects. Furthermore, it must be stressed that the so-called COX-2 inhibitors are not absolutely specific for this isoform of cyclooxygenase, they mere have a preference such as e.g. a 10 fold higher affinity for the COX-2 isoform compared to the COX-1 isoform, and thus they are able to inhibit the GI-protective COX-1 enzyme to some extent.

In situations where pain can be anticipated, such as after a surgical procedure, the analgesic, e.g. an NSAID, may be administered prophylactically before the operation and continued dosing of said NSAID, following a regular schedule in order to minimize pain and inflammation. Patients benefit from receiving optimal NSAID doses, and in some cases very high doses of these analgesic agents are required to efficiently relieve the pain. In conditions of chronic pain, the dosing of palliative agents are of

paramount importance, and since many of the NSAIDs are effective in reducing/preventing/alleviating pain, they reduce the need for opioids, but they are associated with a number of deleterious side-effects, of which the well documented gastrointestinal (GI) irritation is one of the more serious ones. Traditional NSAIDs are also associated with reduced platelet function and thus an increased risk of hemorrhage.

In chronic pain conditions such as Chrohn's disease, migraine, low back pain, cancer pain, arthritis pain associated with e.g. OA or RA, neurogenic pain (pain resulting from damage to the peripheral nerves or to the central nervous system itself), psychogenic pain (pain not due to past disease or injury or any visible sign of damage inside or outside the nervous system), e.g. fibromyalgia and whiplash syndrome a very large systemic burden of NSAIDs can be required to obtain a required palliative effect. Consequently the GI side effects associated with long term NSAID therapy becomes a significant source of morbidity and even mortality in the clinical management of these conditions.

Thus, due to the anticipated side effects of current palliative medications, patients in need of analgesic treatments often receive insufficient doses and/or length of treatment of the palliative agent(s). Therefore there is a pressing need for methods and agents that can improve current pain treatments.

Bisphosphonates strongly decreases osteoclast-mediated bone resorption and are therefore now used extensively in the treatment of patients with metabolic bone diseases characterized by elevated bone turnover such as osteoporosis and Paget's disease. In association with the widespread introduction of these compounds into clinical practice, increased focus have been directed to their adverse effects in the gastrointestinal tract, especially esophageal injury and gastroduodenal ulceration. These side effects may significantly limit the use of these agents, as a required prophylactic use of a bisphosphonate in order to prevent a condition such as osteoporosis would entail the administration of said bisphosphonate to an otherwise healthy subject, who would be prone to treatment withdrawal if apparent GI complications/symptoms are associated with the treatment. In fact it has been suggested that GI side effects represent one of the most common reasons for withdrawal and non-compliance to bisphosphonate treatments.

Bisphosphonates containing an amino group/nitrogen atom in its side chain may exert a direct cytotoxic effect on stomach epithelial cells by inhibiting a key enzyme of the mevalonate pathway responsible for protein prenylation. This is a key cellular process in most cells, and most *in vitro* studies with epithelial cells shows a significant cytotoxic potential of amino-bisphosphonates.

Alendronate and risedronate are the most commonly used orally administered drugs of this type, but newer bisphosphonates such as ibandronate and zoledronate are now being introduced into clinical practice. These compounds all contain a nitrogen atom in their side-chains, which may be especially prone to confer a propensity for GI side effects as outlined above. Shortly after the introduction of alendronate, numerous reports of erosive esophagitis and ulceration appeared. This was thought to be due to contact injury and reflux of acidified alendronate (alendronic acid) into the distal esophagus. Appropriate dosing instructions were subsequently devised, which alleviated this problem to some extent, but was of little effect in those patients with preexisting reflux disease or motility disorders of the esophagus.

Short-term studies of two weeks or less in normal volunteers or patients with osteoporosis with both alendronate and risedronate also revealed acute ulceration in the stomach and duodenum in 5 to 15% of all subjects.

Cytostatic and cytotoxic agents comprise a very heterogeneous group of compounds. Nevertheless, a common site of side effects of this group of therapeutically and/or prophylactically active substances is the GI tract. Common side effects include mucositis (often with ulcerations), such as stomatitis, glossitis, esophagitis and intestinal lesions. [Mitchell EP. Gastrointestinal toxicity of chemotherapeutic agents. Semin Oncol 1993; 19: 566–79. Kennedy L & Diamond J. Assessment and management of chemotherapy- induced mucositis in children. J Pediatr Oncol Nursing 1997; 14: 164–174.] Ulcerative stomatitis is often related to a direct toxic effect on the mucosa, but can also be related to drug-induced neutropenia. Furthermore, anorexia, nausea, vomiting, diarrhea and intestinal lesions and perforations can be seen, and can even be fatal in some instances; such as e.g. have been described with methotrexate or fluorouracil (FU) treatment. [Jacobs C. Use of methotrexate and 5-FU for recurrent head and neck cancer. Cancer Treat Rep 1982; 66: 1925–8.]

Systemically administered glucocorticoids may induce gastrointestinal side effects, including peptic ulcers, gastrointestinal hemorrhage and perforation. Risk factors include the total corticosteroid dose, as well as a previous history of peptic ulceration, advanced malignant disease and concurrent use of NSAIDs. [Ellershaw JE and Kelly MJ. Corticosteroids and peptic ulceration. Palliat. Med.1994: 8(4): 313-9.]

Description of the Invention

It has previously been disclosed in WO2003FR0003279 that one specific strontium salt, strontium ranelate, has the ability to provide relief for gastro-duodenal pain. However, this reference does not disclose the potential of strontium containing compounds such as an inorganic or organic salt of strontium to ameliorate GI toxicity and/or side effects associated with many conventional drugs. Specifically this previous patent does not disclose the pharmaceutical use of a strontium containing product for protection of the stomach epithelial cells.

Accordingly, in the present invention we disclose methods of alleviating or preventing potential GI side effects of a pharmaceutical product intended for oral administration by co-administering with said pharmaceutical product a strontium salt. The present invention relates particularly to the unexpected ability of ionic strontium to protect gastric epithelial cells from damaging effects of other pharmaceutical compounds. Of special relevance to the present invention we have found that the beneficial properties of strontium-containing compounds such as inorganic or organic strontium salts are applicable to all pharmaceutical drug classes known to induce GI side effects. This novel observation is special relevance in the clinical management of chronic diseases such as osteoarthtritis, osteoporosis, certain CNS disorders and certain cancers, where the palliative treatments with pharmaceutical drugs associated with GI side effects will be continued over long time periods due to the chronic nature of the disease, thereby increasing the risk of GI side effects in the individual patient.

Of further relevance for the present invention we have found that the GI-protective properties of strontium are suitable for preventing GI side-effects which can be associated with the intake of many food and drink items, such as certain soft drinks (I.e. coca cola®), fermented food products, food products containing high levels of carboxylic acids e.g. lactic acid, citric acid, amino acids and food items containing high levels of inorganic acids such as phosphoric acid, hydrochloric acid, sulphoric acid and nitric acid. The excellent safety and toxicology profile of strontium enable an

administration of high doses of this ion, i.e. more than 1 g daily, such as more than 2 g daily or more than 3 g daily, and thus a strontium compound according to the invention can be added in sufficient amount to prevent/ameliorate GI related side effects of a food product used in even relatively high quantities.

A strontium salt for a use according to the invention should preferentially be water soluble, and in one embodiment of the present invention, the pH of an aqueous solution of a strontium salt according to the invention has a pH of more than 10. Di-carboxyllic salts of strontium, such as strontium malonate, strontium succinate, strontium oxalate, strontium fumarate, strontium aspartate and strontium glutamate may be especially suited for a pharmaceutical use according to the invention. More generally the invention disclosed in this patent can conveniently be carried out with one or more strontium salts having a water-solubility of at least about 1 g/l and at the most about 100 g/l, which is a range well suited for ensuring the complete solubility of the strontium ion in the stomach. However, strontium salts in general, including both highly soluble (i.e. with solubilities above 100 g/l) and poorly soluble (i.e. with solubilities below 1 g/l) as well strontium salts with intermediate solubility are contemplated to be suitable for use in the present context. Such strontium salts are e.g. the amino acid salts strontium glutamate and strontium aspartate; strontium malonate; strontium pyruvate, strontium maleate and strontium succinate. However, this list is not meant to limit the scope of the invention in any way, and a pharmaceutical composition according to the present invention may be manufactured with many different strontium salts comprising both inorganic and organic counter-ions to the strontium ion.

The inorganic acid for making strontium salts may be selected from the group consisting of boric acid, bromous acid, chloric acid, diphosphoric acid, disulfuric acid, dithionic acid, dithionous acid, fulminic acid, hydrazoic acid, hydrobromic acid, hydrofluoric acid, hydroiodic acid, hydrogen sulfide, hypophosphoric acid, hypophosphorous acid, iodic acid, iodous acid, metaboric acid, metaphosphoric acid, metaphosphorous acid, metasilicic acid, nitrous acid, orthophosphoric acid, orthophosphorous acid, orthosilicic acid, phosphoric acid, phosphinic acid, phosphonic acid, pyrophosphorous acid, selenic acid, sulfonic acid, thiocyanic acid and thiosulfuric acid.

The organic acid may be selected from the group consisting of C_2H_5COOH, C_3H_7COOH, C_4H_9COOH, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_4(COOH)_2$, $C_3H_6(COOH)_2$,

$C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, 2,3,5,6-tetrabromobenzoic acid, 2,3,5,6-tetrachlorobenzoic acid, 2,3,6-tribromobenzoic acid, 2,3,6-trichlorobenzoic acid, 2,4-dichlorobenzoic acid, 2,4-dihydroxybenzoic acid, 2,6-dinitrobenzoic acid, 3,4-dimethoxybenzoic acid, abietic acid, acetoacetic acid, acetonedicarboxylic acid, aconitic acid, acrylic acid, adipic acid, ascorbic acid, aspartic acid (L and D forms), anthranilic acid, arachidic acid, azelaic acid, behenic acid, benzenesulfonic acid, beta-hydroxybutyric acid, benzilic acid, benzoic acid, brassidic acid, carbonic acid, camphoric acid, capric acid, cholic acid, chloroacrylic acid, cinnamic acid, citrric acid, citraconic acid, crotonic acid, cyclopentane-1,2-dicarboxylic acid, cyclopentanecarboxylic acid, cystathionine, decanoic acid, erucic acid, ethanesulfonic acid, ethylenediaminetetraacetic acid, folic acid, formic acid, fulvic acid, fumaric acid, gallic acid, glutaconic acid, gluconic acid, glutamic acid (L an D), glutaric acid, gulonic acid, heptanoic acid, hexanoic acid, humic acid, hydroxystearic acid, ibuprofenic acid, isophthalic acid, itaconic acid, lactic acid, lanthionine, lauric acid (dodecanoic acid), levulinic acid, linoleic acid (cis,cis-9,12-octadecadienoic acid), malic acid, m-chlorobenzoic acid, malic acid, maleic acid, malonic acid, melissic acid, mesaconic acid, methacrylic acid, methanesulfonic acid, monochloroacetic acid, myristic acid, (tetradecanoic acid), nonanoic acid, norvaline, octanoic acid, oleic acid (cis-9-octadecenoic acid), ornithine, oxaloacetic acid, oxalic acid, palmitic acid (hexadecanoic acid), p-aminobenzoic acid, p-chlorobenzoic acid, petroselic acid, phenylacetic acid, p-hydroxybenzoic acid, pimelic acid, propiolic acid, phthalic acid, propionic acid, p-tert-butylbenzoic acid, p-toluenesulfonic acid, pyruvic acid, ranelic acid, sarcosine, salicylic acid, sebacic acid, serine, sorbic acid, stearic acid (octadecanoic acid), suberic acid, succinic acid, tartaric acid, terephthalic acid, tetrolic acid, L-threonic acid, thyronine, tricarballylic acid, trichloroacetic acid, trifluoroacetic acid, trimellitic acid, trimesic acid, tyrosine, ulmic acid, valeric acid, vanilic acid and cylohexanecarboxylic acid.

However, the present invention is not limited to the above-mentioned specific examples of suitable salts, but merely to the general applicability of water-soluble salts of strontium. Some of the known strontium salts (e.g. strontium chloride and strontium hydroxide) have a very high water-solubility. Irrespective of their water-solubility such strontium salts may be used in the combination treatment of the invention. However, in a specific embodiment of the invention the water-solubility of the strontium salt is at the most about 200 g/l such as, e.g. at the most about 150 g/l, at the most about 100 g/l, at the most about 75 g/l, at the most about 50 g/l, at the most about 25 g/l, at the most about 10 g/l, at the most about 5 g/l, at the most about 2.5 g/l, or at the most about 1 g/l

at room temperature (20-25 °C).

In those cases where e.g. a strontium salt having a water-solubility of at the most about 1 g/l (e.g. strontium citrate, strontium carbonate, strontium ranelate, strontium oxalate or strontium hydrogen phosphate), the present inventors have shown that it is possible to delay the appearance of the peak concentration, i.e. the active substance itself may contribute to a delayed release of the strontium ion. This may provide a therapeutic benefit when administered in combination with another pharmaceutical substance with the propensity to induce GI damage as defined in the present invention. Especially if the treatment is given in the evening, it can be advantageous to have a sustained release of the active strontium ion, as this will allow the strontium to exert its GI-protective effect throughout the night. Thus a sustained release of strontium ions throughout the night must be expected to provide the greatest physiological effect.

Moreover, in a specific embodiment of the invention, the strontium salt for use according to the invention may be water soluble, having a water solubility of at least 1 g/l, such as, e.g., at least 5 g/l, at least 10 g/l, at least 20 g/l, at least 30 g/l, at least 40 g/l, at least 50 g/l, at least 60 g/l, at least 70 g/l, at least 80 g/l, at least 90 g/l or at least 100 g/l measured at room temperature, i.e. a temperature of 20-25°C. A more water soluble organic strontium salt comprising an anion with one or more carboxyl-groups may provide significant physiological benefits for a medical use according to the invention.

We have found that such salts, due to the intrinsic alkaline properties of ionic strontium elevates pH when solubilised in aqueous media, such as the gastric juice of the stomach, thereby providing a maximal GI-protective effect. Thus, when administered in combination with other medical agents according to the present invention, such as bisphosphonates, NSAIDs, cytostatic agents or glucocorticoids which are known to be associated with significant gastro-intestinal (GI) adverse events, the strontium salt will have a beneficial effect and serve to prevent or reduce occurrence of GI adverse events.

In one embodiment, the present invention can be carried out by combining in one pharmaceutical composition a strontium compound in combination with one or more other drug products associated with a GI side effect. Such combinations may be administered separately to a subject in need thereof, or they may be given in

combination formulated in the same pharmaceutical dosage unit. Pharmaceutical compositions comprising an effective amount of a strontium containing compound according to the invention and another pharmaceutical product associated with an increased risk or susceptibility to induce a GI side effect may conveniently be formulated with suitable carrier or diluent. Such compositions are preferably in the form of an oral dosage unit or parenteral dosage unit.

Accordingly, in a preferred embodiment, the invention relates to a pharmaceutical composition comprising a) a strontium-containing compound and b) one or more further active substances associated with an increased risk or susceptibility to induce a GI side effect together with one or more physiologically acceptable excipients, wherein the strontium compound a) and the one or more active substances b) may be chosen among the compounds and substances mentioned above.

In a particular embodiment of the invention, the invention may be carried with a pharmaceutical compound consisting of a strontium salt of a pharmaceutically active anions associated with a GI side effect as specified above, such as an NSAID, a bisphosphonate or a cytotoxic agent.

The physiologically acceptable excipients may be a therapeutically inert substance or carrier.

The carrier may take a wide variety of forms depending on the desired dosage form and administration route.

The pharmaceutically acceptable excipients may also be e.g. fillers, binders, disintegrants, diluents, glidants, solvents, emulsifying agents, suspending agents, stabilizers, enhancers, flavors, colors, pH adjusting agents, retarding agents, wetting agents, surface active agents, preservatives, antioxidants etc. Details can be found in pharmaceutical handbooks such as, e.g., Remington's Pharmaceutical Science or Pharmaceutical Excipient Handbook.

The compounds with which the invention is concerned may also be prepared for administration by any route consistent with their pharmacokinetic properties. Especially an oral administration of one or more pharmaceutical compounds according to the invention is relevant, as this is a likely administration route where GI side effects are encountered. The orally administrable compositions may be in the form of tablets,

capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, carboxy-methyl cellulose, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate or magnesium stearate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan mono-oleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or coloring agents.

The solid composition may be in the form of tablets such as, e.g. conventional tablets, effervescent tablets, coated tablets, melt tablets or sublingual tablets, pellets, powders, granules, granulates, particulate material, solid dispersions or solid solutions.
In one embodiment of the invention, the pharmaceutical composition may be in the form of a tablet. The tablet may be coated with a coating that enables release of at least part of the salt in the proximal part of the small intestine, such as e.g. the duodenum and/or the proximal jejunum such as at least 50% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 80% w/w or at least 90% w/w of the total amount of the salt contained in the tablet.

The tablet may have a shape that makes it easy and convenient for a patient to swallow. The tablet may thus e.g. have a rounded or a rod-like shape without any sharp edges. Furthermore, the tablet may be designed to be divided in two or more parts.

For use of the GI-protective properties of a strontium salt according to the invention for prevention of GI side effects of a food product or drink, a strontium compound may simply be added to the food product. This can be done in a variety of different ways, employing common techniques used in the manufacture and/or processing of food and drinks. In principle, a strontium compound can be added to a food item in need thereof either in the primary or secondary processing. Primary processing is the conversion of raw food materials to foods that can be eaten or to ingredients that are used to make edible food products. At its simplest it can be seen as: washing, milling, trimming, squeezing, peeling, ageing and butchery, shelling and chopping. Secondary processing is the conversion of raw ingredients, i.e. the products of primary processing, to edible food products. These procedures may involve one or more of the following: mixing, heating, enrobing, cooling, extruding, drying, layering/dividing, aerating, forming/moulding and fortifying. Of particular relevance to the present invention is the possibility of adding a strontium compound, such as a strontium salt to a food product in need thereof as an integral part of a mixing procedure of said food product.

Definitions

As used in the present invention, a gastrointestinal (GI) side effects may include epigastric/abdominal pain, nausea, vomiting, diarrhea, dyspepsia, bloating, flatulence, anorexia, mucosal erosions and/or inflammation (esophagitis, gastritis, duodenitis, enteritis, colonitis), gastrointestinal hemorrhage including hematemesis, melena and hematochezia, (peptic) ulcerations and GI strictures.

In the present context, a reduction of GI related side effects is intended to denote a decrease in severity and/or incidence among a given treated patient population, Compared to the GI side effects observed after administration of the particular active substance without a simultaneous or sequential administration of a strontium-containing compound. A reduction in GI related side effects according to this definition could thus be construed as a substantial reduction in incidence of any of the GI side effect listed above, such as at least a 10% reduction in incidence or more preferably at least 20 % reduction in incidence or even more preferable a more than 30 % reduction in incidence. A reduction in GI related side effect can also be expressed as a substantial reduction in severity in any of the GI side effects listed above, such as reduction in severity and/or size of an ulcer, mucosal erosion, gastrointestinal hemorrhage including hematemesis, melena and hematochezia, (peptic) ulcerations

and GI strictures or a reduction in severity and/or frequency of vomiting, diarrhea, nausea, epigastric/abdominal pain, bloating, flatulence and anorexia.

As used herein "Chrohn's disease" means an inflammatory condition in the small intestine. It usually occurs in the lower part of the intestine, but can affect any part of the digestive tract, including the mouth, stomach and large intestine. The symptoms of the disease include abdominal pain and frequent bowel movements. Chrohn's disease manifests itself because the inflammation of the intestine causes blockage in the intestine. The disease can also result in sores and ulcers. Digestive problems also occur, as nutrients are unable to be absorbed. This adds to the general GI problems associated with the disease.

As used herein "osteoarthritis" or "OA" means a type of arthritis that is caused by breakdown of cartilage with eventual loss of the cartilage of the joints. The condition may manifest itself in one or only a few joints or it may present as a systemic deterioration of multiple joints. Cartilage is a protein substance that serves as a "cushion" between the bones of the joints. Osteoarthritis is also known as degenerative arthritis or "arthrosis". Although OA is not considered an inflammatory disease, there may be both systemic and/or local elevations in inflammatory activity, which may play a role in OA pathogenesis.

As used herein the term 'Disease Modifying Anti Rheumatic Drug' or DMARD, also known as Disease Modifying anti-OsteoArthritis Drug (DMOAD) comprise a heterogeneous group of compounds Doxycycline, Chondroitin Sulfate, Methotrexate, Leflounomide (ARAVA®, Aventis), Dimethylnitrosamine, azatriopine, chloroquine sulfate, hydroxychloroqine, cyclosporine, minocycline, salazopyrine, penicillamine, aurothiomalate (gold salt), cyclophosphamide, and azathioprine.

Another group of compounds associated with increased risk of GI side effects are the glucocorticoids. These steroid hormones belong to the subgroup of hormones collectively known as corticosteroids. There are two main types of corticosteroids: mieralcorticoids and glucocorticoids. Mineralcorticoids like aldosterone are responsible for the maintenance of salt and fluid balance in the body. Glucocorticoids like cortisol and cortisone affect metabolism and inhibit inflammation. Common glucocorticoids include prednisone, dexamethasone, and hydrocortisone but a number of other synthetic glucocorticoids are used in clinical practice.

For the scope of this invention the class of compounds categorized as non-steroidal antiinflammatory agents (hereinafter NSAID's) comprise molecules such as enolic acis such as piroxicam, tenoxicam and meloxicam, heteroaryl acetic acids such as diclofenac, tolmetin, ketorolac, misoprostol and zomepirac; Indole and indene acetic acids such as indomethacin, mefenamic acid, sulindac and etodolac; Para-amino phenol derivates such as phenacetin and acetaminophen; propionic acids including naproxen, flurbiprofen, fenoprofen, oxaprozin, carprofen, ketoprofen and ibuprofen; fenamates including mefenamic acid, meclofenamate and flufenamic acid; alkanones such as nabumetome; pyrazolones including phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine and kebuzone, salicylates including acetyl salicylate (aspirin), salicylate, salsalate, difunisal, olsalazine, fendosal, sulfasalazine and thiosalicylate COX-2 inhibitors such as celecoxib (tradename CELEBREX® by G. D. Searle & Co., Skokie, Illinois), valdecoxib (tradename BEXTRA® by Pharmacia & Upjohn Company, North Peapack, New Jersey), etoricoxib (tradename ARCOXIA® by Merck & Co., Inc., Whitehouse Station, New Jersey), lumiracoxib (tradename PREXIGE® by Novartis AG, Basel, Switzerland), parecoxib, and rofecoxib (tradename VIOXX® by Merck & Co., Inc., Whitehouse Station, New Jersey), deracoxib (tradename DERAMAXX® by Novartis AG, Basel, Switzerland).

Another class of therapeutically and/or prophylactically active substances, which may be used in a combination treatment according to the present invention, is the cytotoxic agents used in e.g. chemotherapy of a malignant disease. More than 100 chemotherapeutic drugs are currently used to treat different cancers, and many more are in different stages of development, making this a very diverse and heterogeneous group of compounds. Furthermore, cytotoxic agents are often given in combination with surgery and radiotherapy treatments and patients are usually given more than one drug to provide a more effective treatment and reduce the chance of chemo-resistance. These cytotoxic agents usually work by directly binding to the tumor and induce apoptosis of cancer cells. These drug-induced apoptosis events usually relay on two major intrinsic apoptotic pathways: the ligation of cell surface death receptors and mitochondrial release of cytochrome c. Activation of both pathways will lead to an array of reaction that will activate caspase proteins and eventually, cell death. However, when administered by the oral route to a mammal in need thereof, these cytotoxic agents may mediate a similar effect on cells of the stomach and intestinal epithelia, and thus they may with advantage be given in combination with a strontium compound to

ameliorate such side effects. The following list of common cytotoxic agents are provided to indicate the type of agents with potential medical use as claimed in this invention, but the list is not meant to limit the scope of the invention. Common cytotoxic treatments comprise the following agents:

paclitaxel (Taxol), docetaxel (Taxotere), carboplatin (Paraplatin), cisplatin (Platinol), oxaliplatin (Eloxatine), gemcitabine (Gemzar), irinotecan (Camptosar), capecitabine (Xeloda), doxorubicin (Adriamycin), epirubicin (Ellence), cyclophosphamide (Cytoxan), etoposide (Vepesid), vinorelbine (Navelbine), fludarabine (Fludara), mitoxantrone (Novantrone), procarbazine (Natulan, Matulane), vinblastine (Velben, Velban, Velsar), mitomycin (Mutamycin), vindesine (Eldesine), vincrestine (Oncovin, Vincasar, Vincrex), teniposide (Vumon), mycophenolate mofetil (CellCept), azathioprine (Imuran), cyclophosphamide (Cytoxan), methotrexate (MTX, Rheumatex), cyclosporin A (Sandimmune, Neoral), 5-Fluorouracil (Adrucil), Tetrathiomolybdate, bleomycin sulfate, cytarabine, dacarbazine, dactinomycin, daunorubicin, procarbazine, vincristine

Examples

Example 1

Pharmaceutical composition containing alendronate and a strontium compound

Tablet formulation

Ingredient	Amount (mg) /tablet
Alendronate	10 mg
Strontium malonate	200 mg
Lactose Ph.Eur.	100 mg
Corn starch Ph.Eur. (for mixing)	15 mg
Corn starch Ph.Eur. (for paste)	15 mg
Magnesium Stearate Ph.Eur. (1%)	10 mg
Total	350 mg

Alendronate and strontium malonate, lactose and cornstarch (for mixing) are blended to uniformity. The cornstarch for paste is suspended in 200 ml of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders (wet granulation). The wet granules are passed through a number 8 hand screen and dried at 80°C. After drying, the granules are lubricated with 1 % magnesium stearate and pressed into a tablet. Such tablets can be administered to a human subject in need thereof, such as an OA or RA patient, from one to two times daily

Example 2

Pharmaceutical composition containing methotrexate and a strontium compound

Tablet formulation

Ingredient	Amount (mg) /tablet
Methotrexate	20 mg
Strontium malonate	200 mg
Lactose Ph.Eur.	100 mg
Corn starch Ph.Eur. (for mixing)	15 mg
Corn starch Ph.Eur. (for paste)	15 mg
Magnesium Stearate Ph.Eur. (1%)	10 mg
Total	360 mg

The tablets are prepared as described in Example 1.

Example 3

Pharmaceutical composition containing naproxen and a strontium compound

Tablet formulation

Ingredient	Amount (mg)
Naproxen	250 mg
Naproxen	250 mg
Strontium malonate	210 mg
Lactose Ph.Eur.	100 mg
Corn starch Ph.Eur. (for mixing)	15 mg
Corn starch Ph.Eur. (for paste)	15 mg
Magnesium Stearate Ph.Eur. (1%)	10 mg

The tablets are prepared as described in Example 1.

Example 4

Pharmaceutical composition containing celecoxib and a strontium compound

Tablet formulation

Ingredient	Amount (mg)
Celecoxib	200 mg
Strontium malonate	200 mg
Lactose Ph.Eur.	100 mg
Corn starch Ph.Eur. (for mixing)	15 mg
Corn starch Ph.Eur. (for paste)	15 mg
Magnesium Stearate Ph.Eur. (1%)	10 mg
Total	540 mg

The tablets are prepared as described in Example 1.

Example 5

Treatment with strontium malonate and naproxen

The aim of this experiment is to evaluate palliative effects as well as the presence of GI side effects in two groups of patients treated with either a combination of a strontium compound and naproxen alone. The palliative treatment regiments are given to patients with a clinical diagnosis of mild to moderate OA. The patients are selected to comprise OA patients with a clinical diagnosis of OA at either the hip and/or knee joints with a well defined clinical presentation of the disease. Pain and function of the patients are evaluated with a standardized scoring system (WOMAC score) at the initiation of the study and after 2, 4 and 6 weeks. The presence of gastric irritations, including ulcers is determined by upper endoscopic examinations performed at baseline and at study termination. The response in the treated patients is compared to the response in a similar placebo treated group.

Study protocol and patients

Briefly described the study cohort consists of patients above 50 years of age (mean about 59 years) with OA of the medial femoro-tibial compartment and/or the hip diagnosed according to the clinical and radiological criteria of the American College of Rheumatology. The patients are recruited at a clinic of osteoarthritic rehabilitation. The severity of their disease corresponds to grade 2 or 3 on the Kellgreen and Lawrence scoring scale, with average disease duration of about 5 years. They are divided in two groups equally sized treated with either 200 mg naproxen and 1200 mg strontium malonate or 200 mg naproxen alone for six weeks. Urine samples are obtained at baseline and after 12 month as second morning void samples without dietary restrictions.

The primary outcome measures in the trial are the presence of upper GI damage determined by endoscopic examination. As secondary endpoints the presence of disease symptoms is assessed by the Western Ontario and McMasters Universities osteoarthritis index (WOMAC, VA 3.0 version) performed bi-weekly. As a secondary outcome measures biomarkers of bone and cartilage turnover is measured. For the later purpose, urine samples are obtained at baseline and after 2 and 6 weeks and measured for the presence of cartilage degradation products using the CartiLaps assay specific for C-telopeptide fragments of articular cartilage derived collagen type II, and the urine CrossLaps ELISA (CTX-I) specific for osteoclast generated degradation products of bone matrix type I collagen.

CTX-II measurements

Urinary levels of collagen type II C-telopeptide fragments are measured by the CartiLaps ELISA assay. The assay uses a highly specific monoclonal antibody MAbF46 specific for a 6-amino acid epitope (EKGPDP) derived from the collagen type II C-telopeptide. The assay is performed essentially as described by the manufacturer (Nordic Bioscience, Herlev, Denmark). All samples are measured in duplicates. All samples from one individual are measured in the same ELISA plate and two control samples are included on each ELISA plate. Average intra- and inter- assay CV is determined. Three genuine control samples are included on each microtitre plate and if measurements deviate more than ±20% from the predetermined values the plate is re-measured.

The concentration of the CTX-II ELISA (ng/l) is standardized to the total urine creatinine (mmol/l): concentration/creatinine = ng/mmol. Creatinine concentration is measured using a Cobas MIRA analyzed according to the manufactures instructions (Roche Diagnostics, Basel, Switzerland).

Of importance for the present invention, the study demonstrates if the combination strontium and naproxen prevent the occurrence of GI side-effect observed in human subjects when administering naproxen alone.

Claims

1. A method of alleviating, reducing and/or preventing gastrointestinal (GI) side effects induced by a therapeutically and/or prophylactically active pharmaceutical substance or a food product in an animal including a mammal, the method comprising administration of one or more strontium containing compounds.

2. A method according to claim 1, the method comprising administration of the therapeutically and/or prophylactically active substance or food product responsible for/associated with the GI side effects together with the one or more strontium containing compounds.

3. A method according to claim 2, wherein the administration of i) the therapeutically and/or prophylactically active substance or food product responsible for/associated with the GI side effects and ii) the one or more strontium containing compounds is substantially simultaneously or sequentially.

4. A method according to any of claims 1-3, wherein the administration is via the oral route.

5. A method according to any of the preceding claims, wherein the side effects are selected from the group consisting of epigastric/abdominal pain, nausea, dyspepsia, vomiting, diarrhea, flatulence, anorexia, mucosal erosions and/or inflammation (esophagitis, gastritis, duodenitis, enteritis), gastrointestinal hemorrhage including hematemesis, melena and hematochezia, (peptic) ulcerations, GI strictures, and stomach or bowel irritation.

6. A method according to any of the preceding claims, wherein the animal is a human.

7. A method according to any of claims 1-5, wherein the animal is a domestic animal such as a dog (*canis familiaris*), cat (*felix domesticus*), cow (*bos Taurus*), horse (*equus caballus*), donkey or pig (*sus scrofa*).

8. A method according to any of the preceding claims, wherein the prevention of GI side-effects is obtained by using a strontium salt having a pH above 10 when dissolved

in water at a temperature between 20 – 25 °C and in a concentration of at the most 1g/l.

9. A method according to any of the preceding claims, wherein the strontium containing compound has a solubility corresponding to a range of from about 1 to about 100 g/l in water at a temperature between 20 – 25 °C.

10. A method according to any of the preceding claims, wherein the strontium containing compound is selected from the group of organic strontium salts comprising: strontium malonate, strontium succinate, strontium fumarate, strontium ascorbate, strontium aspartate in either L and/or D-form, strontium glutamate in either L- and/or D-form, strontium pyruvate, strontium tartrate, strontium glutarate, strontium maleate, strontium methanesulfonate, strontium benzenesulfonate and strontium ranelate, strontium acetyl salicylate, strontium oxalate, strontium carbonate, strontium chloride, strontium phosphate, strontium sulphate, strontium hydroxide, strontium citrate, strontium lactate and strontium threonate.

11. A method according to any of the preceding claims, wherein the strontium containing compound is a strontium salt that comprises an organic anion with one or more carboxylic acid groups.

12. A method according to any of the preceding claims, wherein the therapeutically and/or prophylactically active substance responsible for/associated with the GI side effects is an NSAID selected from the group comprising enolic acis such as piroxicam, tenoxicam and meloxicam, heteroaryl acetic acids such as diclofenac, tolmetin, ketorolac, misoprostol and zomepirac; Indole and indene acetic acids such as indomethacin, mefenamic acid, sulindac and etodolac; Para-amino phenol derivates such as phenacetin and acetaminophen; propionic acids including naproxen, flurbiprofen, fenoprofen, oxaprozin, carprofen, ketoprofen and ibuprofen; Sulphonanilides such as Nimesulide; fenamates including mefenamic acid, meclofenamate and flufenamic acid; alkanones such as nabumetome; pyrazolones including phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine and kebuzone, salicylates including acetyl salicylate (aspirin), salicylate, salsalate, difunisal, olsalazine, fendosal, sulfasalazine and thiosalicylate; paracetamol; or a pharmaceutically acceptable salt thereof

13. A method according to claim 12, wherein the NSAID is acetyl salicylic acid (ASA) and the daily dose of ASA is in the range from 1 to 3000 mg/day such as, e.g., from 75 to 320 mg/day, such as 75 mg once daily, 81 mg once daily, 160 mg once daily, 300 mg once daily or 160 mg twice daily.

14. A method according to any of the preceding claims, wherein the therapeutically and/or prophylactically active substance is a selective COX-2 inhibitor that has at least a 10 fold higher affinity for the COX-2 enzyme compared to the COX-1 enzyme.

15. A method according to claim 14, wherein the selective COX-2 inhibitor is selected from the group consisting of rofecoxib (Vioxx) dosed in the range corresponding to 10-50 mg/day, valdecoxib (Bextra) dosed in the range corresponding to 5-20 mg/day, celecoxib (Celebrex) dosed in the range corresponding to 100-500 mg/day, etoricoxib (Arcoxia) dosed in the range corresponding to 25-150 mg/day, lumiracoxib (Prexige) dosed in the range corresponding to 100-500 mg/day, parecoxib (Dynastat) dosed in the range corresponding to 20-200 mg/day, deracoxib (Deram) dosed in the range corresponding to 10-200 mg/day , tiracoxib, meloxicam, nimesolide, (1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-l-hydroxy-6,6dimethyl-6H-dibenzo[b,d]pyran carboxylic acid (CT-3), 2(5H)-Furanone, 5,5-dimethyl (l-methylethoxy) [4(methylsulfonyl)phenyl]- (DFP); Carprofen (RIMADYL), (Acetyloxy)-benzoic acid, 3-[(nitrooxy)methyllphenyl ester (NCX4016), P54 (CAS Reg. No. 130996 0) 2,6-Bis(1,1-dimethylethyl) [(E)-(2-ethyl-1,1-dioxo isothiazolidinylidene)methyl]phenol (S-2474), 5(R)-Thio sulfonamide-3(2H)-benzofuranone (SVT-2016) and N-[3-(Fonnyl-amino) oxo phenoxy-4H benzopyran yl] methanesulfonamide ("T-614"); or a pharmaceutically acceptable salt thereof.

16. A method according to any of the preceding claims, wherein the therapeutically and/or prophylactically active substance is a cytotoxic agent selected from the group consisting of antineoplastic agents comprising paclitaxel (Taxol), docetaxel (Taxotere), carboplatin (Paraplatin), cisplatin (Platinol), oxaliplatin (Eloxatine), gemcitabine (Gemzar), irinotecan (Camptosar), capecitabine (Xeloda), doxorubicin (Adriamycin), epirubicin (Ellence), cyclophosphamide (Cytoxan), etoposide (Vepesid), vinorelbine (Navelbine), fludarabine (Fludara), mitoxantrone (Novantrone), methotrexate, procarbazine (Natulan, Matulane), vinblastine (Velben, Velban, Velsar), mitomycin (Mutamycin), vindesine (Eldesine), vincrestine (Oncovin, Vincasar, Vincrex), teniposide (Vumon).

17. A method according to any of the preceding claims, wherein the therapeutically and/or prophylactically active substance is a glucocorticoid such as prednisolone, prednisone, methylprednisolone, betamethasone, hydrocortisone, cortisone, triamcinolone, dexamethasone, beclomethasone, budesonide, deoxycortone or fludrocortisone, prednisone dosed in the range corresponding to 0.5 – 15 mg/day, dexamethasone dosed in the range corresponding to 1 – 20 mg/day, or hydrocortisone dosed in the range corresponding to 1 – 25 mg/day.

18. A method according to any of claims 1-7 where a strontium containing compound is administered to a patient with a joint disease in combination with a DMARD selected from the group comprising Doxycycline, Chondroitin Sulfate, Methotrexate, Leflounomide (ARAVA®, Aventis), Dimethylnitrosamine, azatriopine, hydroxychloroqine, cyclosporine, minocycline, salazopyrine, penicillamine, aurothiomalate (gold salt), cyclophosphamide, and azathioprine.

19. A method according to any of the preceding claims, wherein the therapeutically and/or prophylactically active substance is a bisphosphonate selected from the group consisting of ibandronate, dosed in the range corresponding to 1 – 5 mg/day, zoledronate dosed in the range corresponding to 0.01 – 0.5 mg/day, alendronate, dosed in the range corresponding to 5 – 25 mg/day, risedronate, dosed in the range corresponding to 2.5 – 10 mg/day, ethidronate dosed in the range corresponding to 100 – 500 mg/day, chlodronate dosed in the range corresponding to 25 – 100 mg/day, tiludronate and pamidronate.

20. A method according to any of the preceding claims, wherein the strontium containing compound after administration can increase aqueous/intestinal pH with at least 0.5 such as at least 1.0 or at least 2.0 pH units.

21. A method according to any of the preceding claims, wherein the therapeutically and/or prophylactically active substance or food product responsible for/associated with the GI side effects and the one or more strontium containing compounds are is administered as a single composition.

22. A method according to any of the preceding claims, wherein the therapeutically and/or prophylactically active substance or food product responsible for/associated with the GI side effects and the one or more strontium containing compounds are

administered as separate compositions

23. A method according to any of the preceding claims, wherein the strontium containing compound is administered in the form of a food product, such as a solid food, a drink, a snack or other edible product.

24. A pharmaceutical composition for use in a method as defined in any of claims 1-22 in the form of a tablet.

25. A pharmaceutical composition according to claim 24, wherein the tablet is coated with a coating that enables release of at least part of the strontium containing compound in the proximal part of the small intestine, such as e.g. the duodenum and/or the proximal jejunum such as release of at least 50% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 80% w/w or at least 90% w/w of the total amount of the strontium containing compound contained in the tablet in the proximal part of the small intestine.